EXPRESS MAIL CERTIFICATE

Date_____ Label No._____
I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

_____ _____
Name (Print) Signature

**PLEASE CHARGE ANY DEFICIENCY UP TO $300.00 OR CREDIT ANY EXCESS IN THE FEES DUE WITH THIS DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04-0100**

Customer No.: 07278

PATENT TRADEMARK OFFICE

Docket No: 3671/0J107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Armin Prasch et al.

Serial No.: 09/845,682 Art Unit: 16450

Confirmation No.: 2295

Filed: April 26, 2001 Examiner: Jean C. Witz

For: Fibrin tissue adhesive formulation and process for its preparation

---

**DECLARATION UNDER RULE 132**

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

PETER C. SCHMIDT, declares as follows:

1. I am a Professor at the Pharmaceutical Institute, Tübingen University, located at Auf der Morgenstelle 8, D-72076 Tübingen, Germany.

2. I have read the information set forth in U.S. Patent Application No. 09/845,682 ('682

Application) and WO 97/44015 ('44015 Application).

3. I have been asked by Applicants, through their representative, Pfenning, Meinig & Partner, to explain the differences between U.S. Patent Application No. 09/845,682 and WO application 97/44015 in a comparative assessment.

4. The '682 Application and the '44015 Application both make use of fibrinogen and thrombin as active ingredients for a fibrin adhesive formulation, with calcium chloride, albumin, sugar or sugar substitutes as other ingredients.

5. According to the '44015 Application, the ingredients are dissolved in water and then subjected to spray drying at an inlet temperature of 100 °C and an outlet temperature of 65 °C using a Schlick nozzle of type 970/0 with an atomizing pressure of 1 bar. In the '44015 application, thrombin and fibrinogen are processed separately because processing together in solution would initiate a premature reaction. Thus, both active ingredients are subjected to spray drying with a so-called pneumatic nozzle from solution.

6. Spray-drying processes of solutions under conditions mentioned above result in extremely fine powders with particles of about 1 to 20 μm. Accordingly, claim 8 of the '44015 Application logically sets forth particles, wherein 90% are between 10 and 20 μm. Although claim 1 of the '44015 Application refers to soluble, free-flowing microparticles, the free-flowing nature of their product is doubtful due to the small particle size.

7. Figure 1, attached hereto, shows spray-dried microparticles prepared from a solution of bearberry leaf extract. The particle size is in the range of 1 to 10 μm. The hollow-sphere structure is clearly evident from the blow hole in the particle in the middle of the picture. The picture is characteristic for all spray-dried products prepared from solution using a pneumatic nozzle. Hollow microspheres in the range of 1 to 20 μm are always produced and form cohesive powders with a very low apparent density. These powders are difficult to handle, are cohesive and cause problems during further processing, transport and storage. A further disadvantage of the '44015 Application is that in spray drying from solution it is possible only to process the individual components (fibrinogen and thrombin) separately, and the spray-dried products must then be mixed. It is thus impossible from the outset to prepare a product containing both substances together.

8. By contrast, the '682 Application describes granules prepared in a fluidized bed. This entails, for example, an active ingredient concentrate being sprayed from aqueous solution onto a crystalline starting material consisting of a sugar or sugar alcohol. In addition, barrier layers can be applied. The resulting granules usually have a particle size of 30 to 500 μm, preferably 40 to 200 μm. They are thus free-flowing, can be spread, and are rapidly dissolving due to its hydrophilic nature.

9. In principle, the fluidized bed technology makes the following variations possible:

1. Preparation of thrombin-containing granules.

2. Preparation of fibrinogen-containing granules.

3. Preparation of a mixed product composed of the two granules from 1 and 2.

4. Preparation of fibrinogen granules which are subsequently provided with a barrier layer onto which thrombin can be applied in the outer layer. Polyvinylpyrrolidone and water-soluble cellulose derivatives or carbohydrates are suitable as a barrier layer.

5. Preparation of granules with one of the two active ingredients from aqueous solution and subsequent application of the second active ingredient suspended in an organic solvent. Use of an organic solvent in the second stage avoids premature coagulation between fibrinogen and thrombin.

10. The resulting fluidized bed granules are dust-free, with the particle sizes previously specified, free-flowing and easily metered. The morphology of these particles is depicted in Figure 2 for fibrinogen fluidized bed granules and in Figure 3 for thrombin fluidized bed granules. Both Figures are attached. The particles exhibit the typical slightly porous granule structure. They are not hollow spheres.

11. The spray-drying process described in the '44015 Application leads to microparticles with sizes in the range from 1 to 20 μm having hollow-sphere characteristics. They are easily crushed, cohesive and cause difficulties during further processing, transport and storage.

12. The granules described in the '682 Application are compact, slightly porous solid

particles not having hollow-sphere characteristics. The size range is preferably from 40 to 200 μm, resulting in a dust free product with improved flow properties. The granules have rapid dissolution characteristics.

13. Using spray drying, it is possible only to process thrombin and fibrinogen separately. The two active ingredients cannot be processed together in aqueous solution because of coagulation. The separate granules must subsequently be mixed in the desired ratio. By contrast, fluidized bed granulation makes it possible to prepare both separate granules of the two active ingredients and combination products. Possibilities in the preparation of combination products are both preparation without a barrier layer through the use of the second active ingredient in an organic suspension, and preparation with inclusion of a barrier layer and thus separation of the two active ingredients on the same core.

14. Spray drying from solution with pneumatic nozzles always results in microparticles having sizes in the range of 1 to 20 μm with a hollow-sphere structure. Such particles are usually not free-flowing and are cohesive. Granulation preferentially affords particles with sizes of the order of 40 to 200 μm, and coarser particle size distributions can also be achieved using appropriate process parameters. These coarse distributions have improved flow properties, reduced dust formation and rapid dissolution.

15. In summary, therefore, it must be stated that there are considerable differences between the two products, and the '682 Application represents a clear advance over the '44015

Application.

16. I declare further that statements made in this Declaration are of my own knowledge and are true and that all statements made on information and belief are believed to be true and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed on January 29, 2003

P. C. Schmidt

Prof. P. C. Schmidt

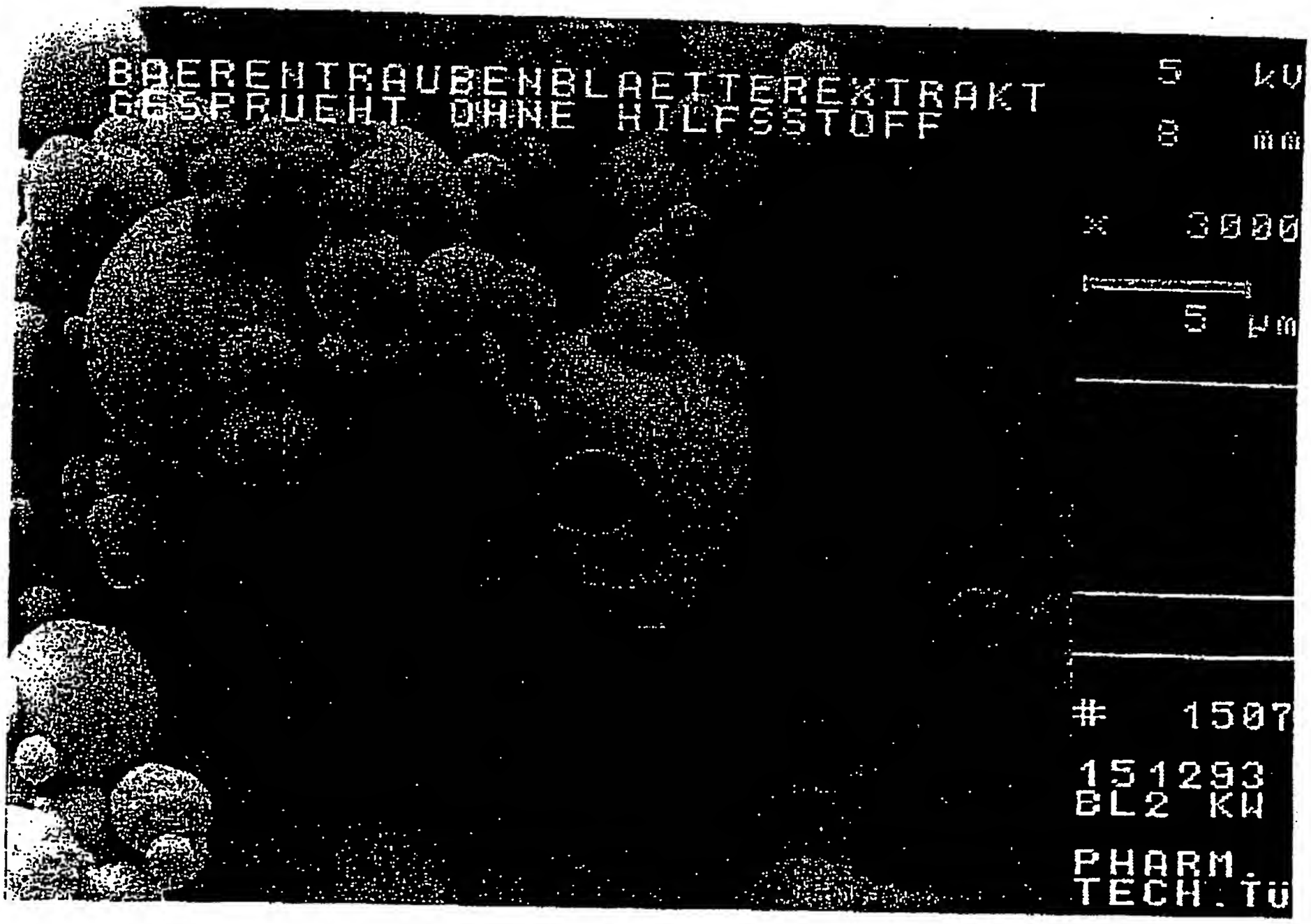


Figure 1: Spray-dried microparticles of barberry leaf extract (comparison product)


Figure 2: Fluidized bed fibrinogen granules

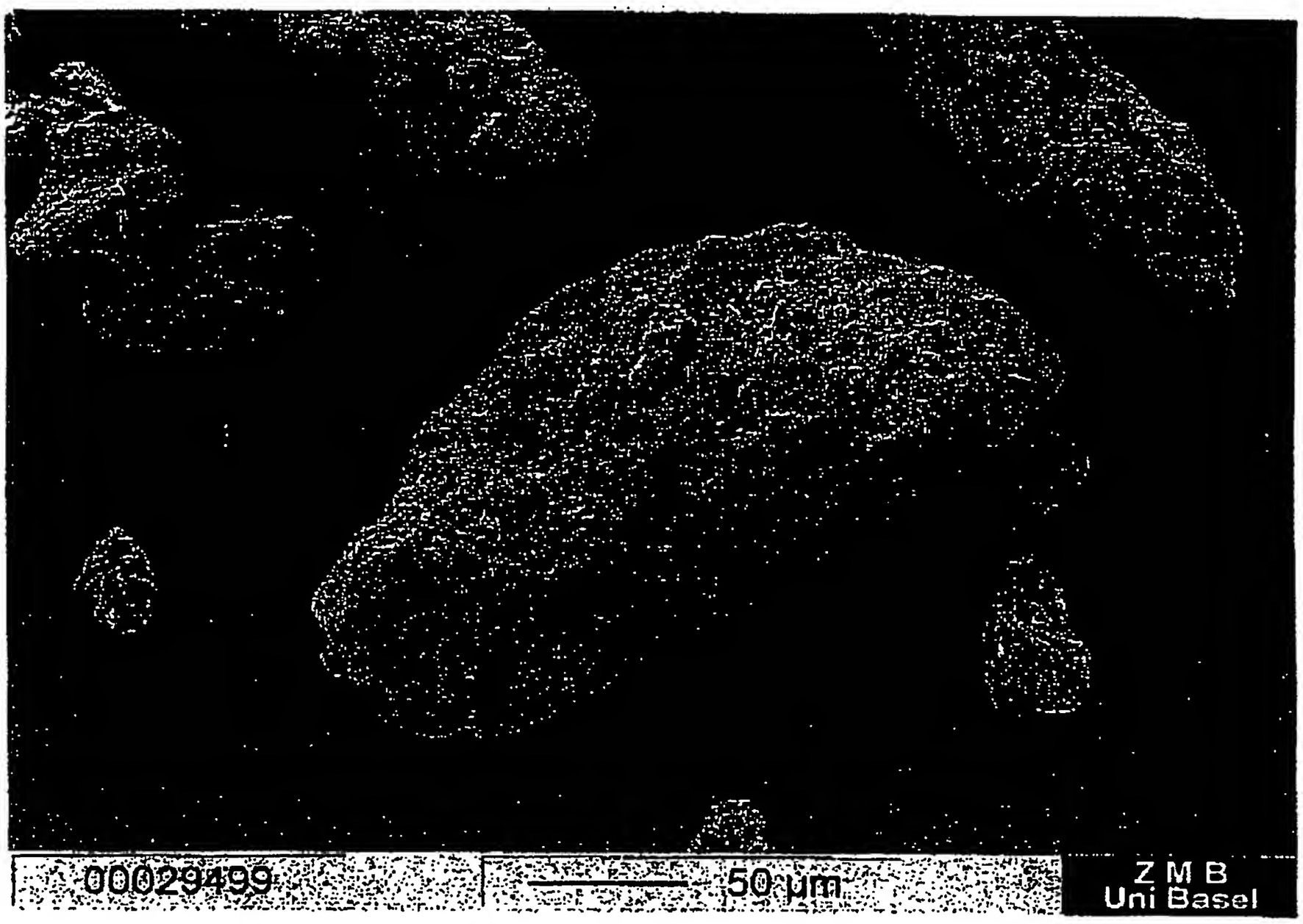


Figure 3: Fluidized bed thrombin granules

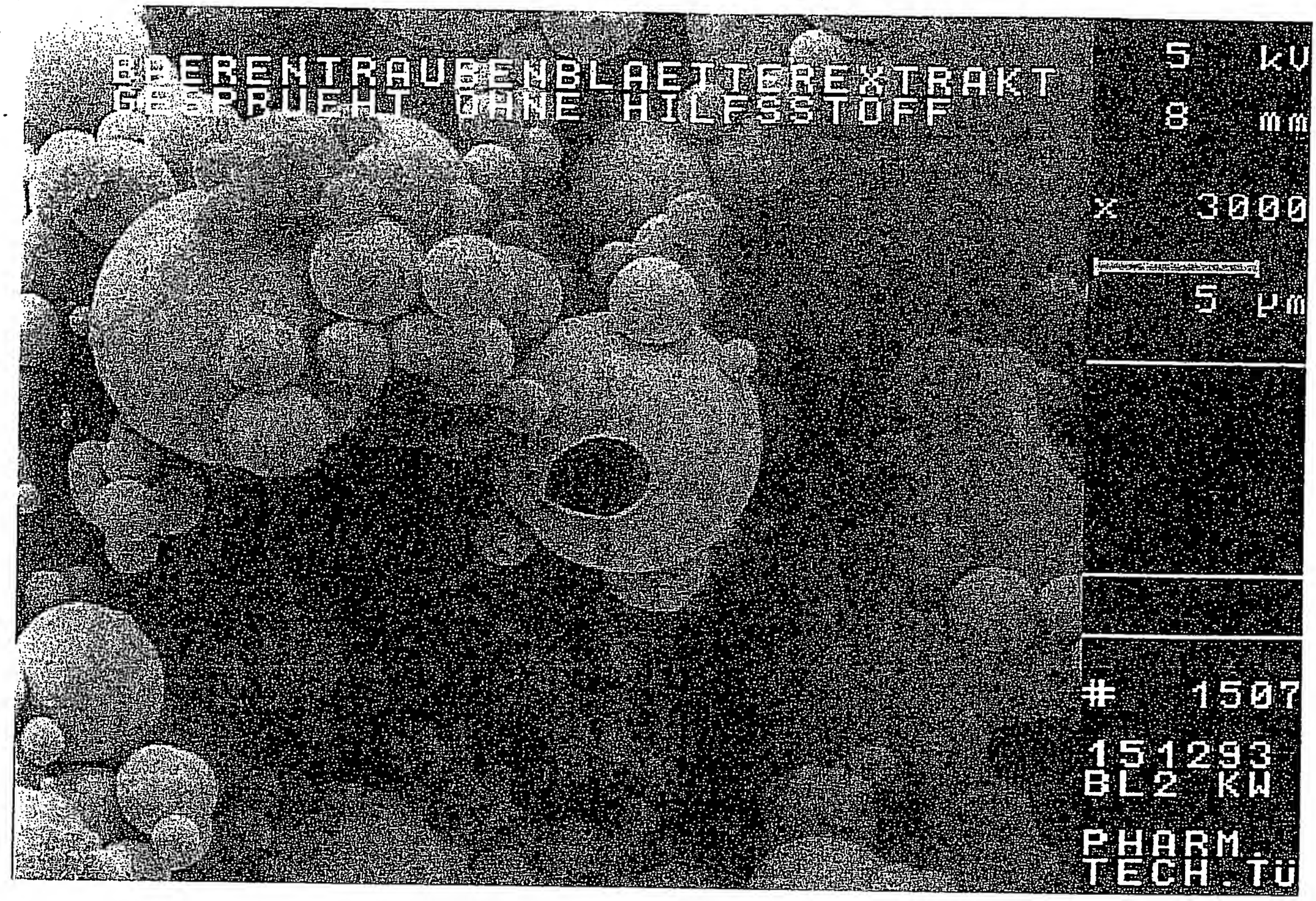


Abbildung 1: Sprühgetrocknete Mikropartikeln aus Bärentraubenblätter-Extrakt (Vergleichspräparat)

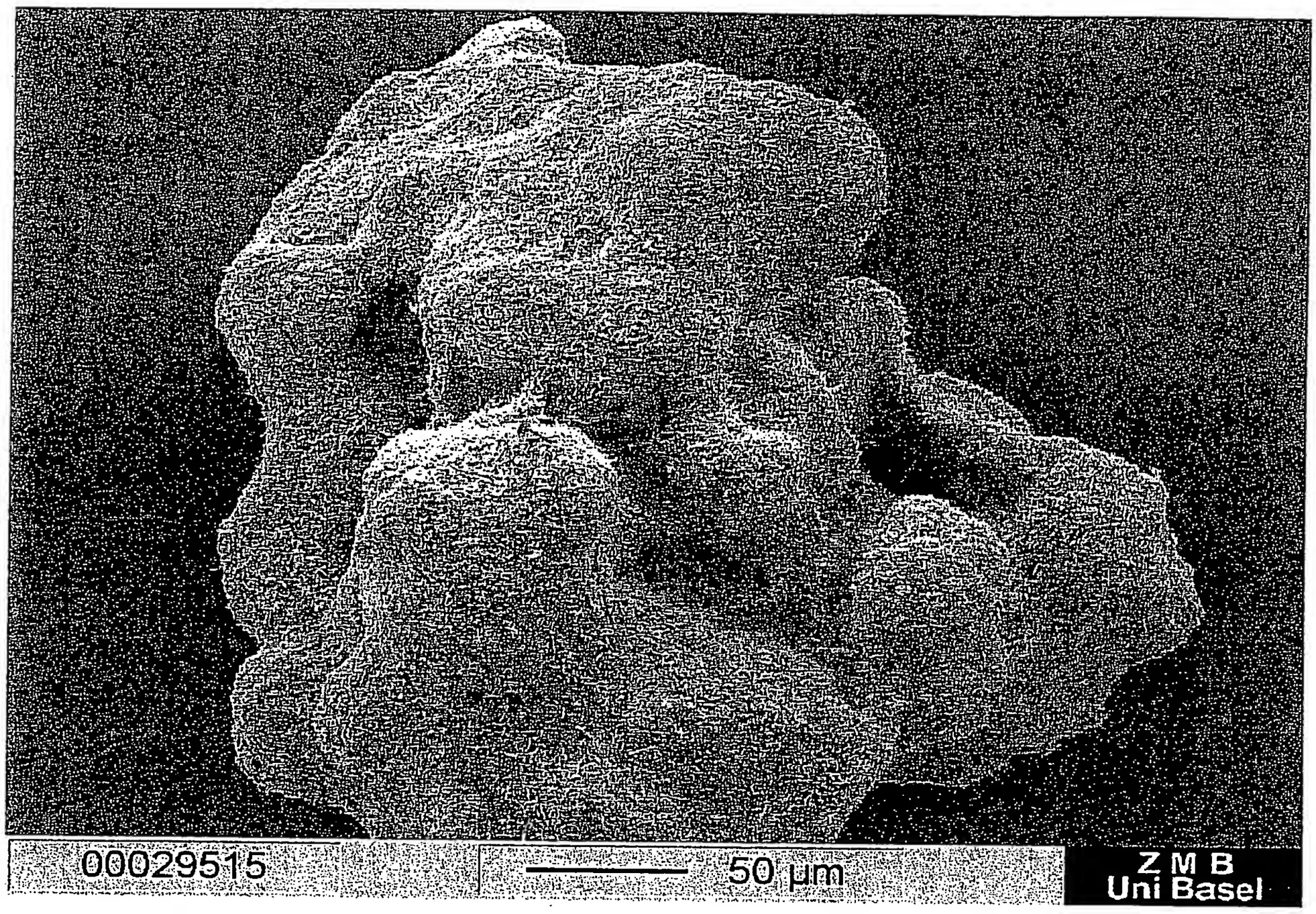


Abbildung 2: Wirbelschichtgranulat eines Fibrinogen-Granulates

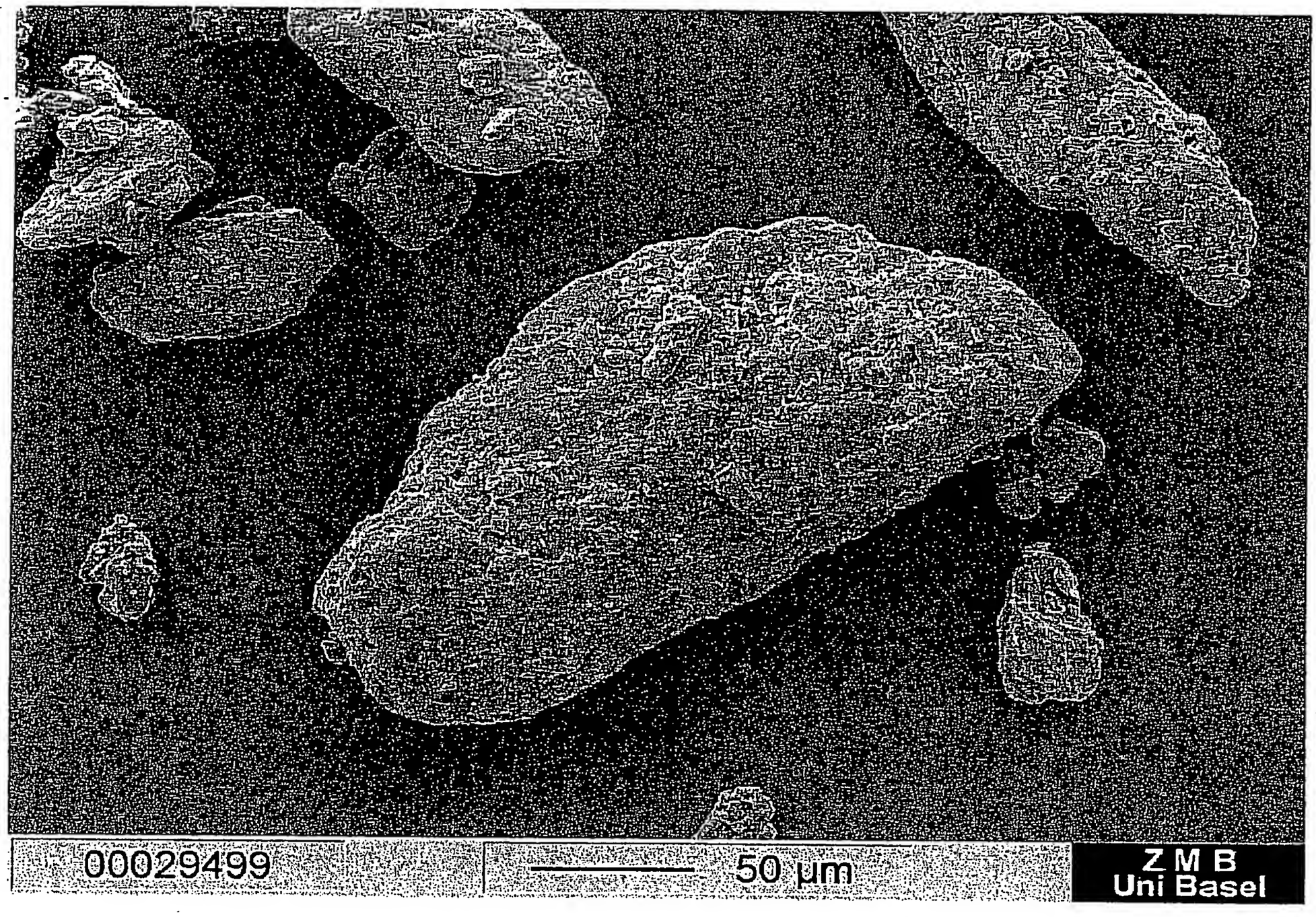


Abbildung 3: Wirbelschichtgranulat eines Thrombin-Granulates

# Curriculum Vitae

| | |
|---|---|
| **Peter Christian Schmidt** | born on March 4, 1940 |
| **1964 - 1967** | Study of Pharmacy at the University of Erlangen/Nürnberg, Germany |
| **1967 - 1970** | University of Hamburg, Ph. D. Thesis: "The determination of micelle molecular weights of tensides by gel chromatography", supervisor: Prof. Dr. Heinz Sucker |
| **1970 - 1981** | Research and development in the pharmaceutical industry in Germany and Switzerland, main interests:development of solid dosage forms and medicaments from plants |
| **1981 – 1988** | Professor for Pharmaceutical Technology at the University of Marburg |
| **1984 – 1985** | Dean of the Faculty |
| **1984 – 1988** | Director of the Institute at the University of Marburg |
| **since 1988** | Professor for Pharmaceutical Technology at the University of Tuebingen, Germany |
| | Head of the Department for Pharmaceutical Technology |
| **1991 - 1994** | Director of the Institute for Pharmacy |
| **1992 - 1994** | Dean of the Faculty for Chemistry and Pharmacy |
| **Research activities** | Instrumentation of tablet machines, development of solid dosage forms and new tablet excipients, dry powder inhalations, film coating, development and stabilization of medicaments from plants, supercritical fluid extraction |
| **Publications** | around 190 papers, 20 patents and book chapters, |
| | two books: „Phytopharmaceutical Technology“ and „Wirk- und Hilfsstoffe für Rezeptur, Defektur und Großherstellung“ |
| **Other activities** | Member of several associations like AAPS, German Pharmaceutical Association, International Association for Pharmaceutical Technology (APV), head of two working groups within the last two associations for several years. Member of the Scientific Committee of the German Advisory Board of Pharmacist, Adjunct professor at the University of Cincinnati, Visiting professor at he Universities of Addis Ababa, Ethiopia, Porto Alegre and Natal, Brazil, University of Lisbon, Portugal and University of Ljubljana, Slovenia |
| **Present address** | University of Tuebingen<br>Dept. of Pharmaceutical Technology<br>Auf der Morgenstelle 8<br>D-72076 Tuebingen (Germany) |

Tuebingen, January 29, 2003
Lebeneng.doc

**Publikationsliste Prof. Dr. P. C. Schmidt**

1998 bis 2002

M. A. Moser, M. Krumme, P. C. Schmidt
Flexure Test of Tablets
Pharmazie, 53, 46-51 (1998)

B. Rotthäuser,G. Kraus, P. C. Schmidt
Vergleich von Schmiermitteln für Brausetabletten mittels Hauptkomponentenanalyse
Pharm. Ind., 60, 541-546 (1998)

K. G. Wagner, M. Krumme, P. C. Schmidt
Investigation of pellet-distribution in single tablets via image analysis
Eur. J. Pharm. Biopharm., 47, 79-85 (1999)

T. Gebre-Mariam, P. C. Schmidt
Some Physico-chemical Properties of Dioscorea Starch from Ethiopia
Starch/Stärke, 50, 241-246 (1998)

C. A. Scheef, P. C. Schmidt
Influence of surface acidity of excipients on the solid state stability of pirenzepine
S. T. P. Pharma Sci., 8, (2), 91-97 (1998)

C. A. Scheef, D. Oelkrug, P. C. Schmidt
Surface acidity of Solid Pharmaceutical Exipients III. Excipients for solid dosage forms
Eur. J. Pharm. Biopharm., 46, 209-213 (1998)

H. M. Cabral Marques, P. C. Schmidt
Simultaneous determination of lactose and sodium cromoglycate in a dry powser inhalation formulation
Pharmazie, 54, 785-786 (1999)

F. Waimer, M. Krumme, P. Danz, U. Tenter, P. C. Schmidt,
A novel method for the detection of sticking of tablets,
Pharm. Dev. Technol., 4, 359-367 (1999)

F. Waimer, M. Krumme, P. Danz, U. Tenter, P. C. Schmidt
A model to investigate the influence of engravings on the sticking of tablets
Pharm. Dev. Technol., 4, 369-375 (1999)

H. C. J. Orth, C. Rentel, P. C. Schmidt
Isolation, Purity Analysis and Stability of Hyperforin as a Standard Material from Hypericum Perforatum L.
J. Pharm. Pharmacol., 51, 193-200 (1999)

A. Fetscher, P. C. Schmidt
Einfluß von wasserlöslichen und wasserunlöslichen Weichmachern auf die thermomechanischen Eigenschaften von magensaftresistenten Filmüberzügen
Pharm. Ind., 61, 69-73 (1999)

K. Rocksloh, F.-R. Rapp, S. Abu Abed, W. Müller, M. Reher, G. Gauglitz, P. C. Schmidt
Optimization of crushing strength and disintegration time of a high dosed plant extract tablet by neural networks
Drug Dev. Ind. Pharm., 25, 1015-1025 (1999)

H. C. J. Orth, H. Hauer, C. A. J. Erdelmeier, P. C. Schmidt
Orthoforin: The main degradation product of hyperforin from Hypericum perforatum L.
Pharmazie, 54, 76-77 (1999)

H. Rey, K. G. Wagner, P. Wehrlé, P. C. Schmidt
Development of matrix based theophylline sustained-release microtablets
Drug Dev. Ind. Pharm., 26, 21-26 (2000)

A. Adam, L. Schrimpl, P. C. Schmidt
Some physicochemical properties of mefenamic acid
Drug Dev. Ind. Pharm., 26, 477-487 (2000)

A. Adam, L. Schrimpl, P. C. Schmidt
Factors influencing capping and cracing of mefenamic acid tablets
Drug Dev. Ind. Pharm., 26, 489-497 (2000)

K. Wöstheinrich, P. C. Schmidt
Evaluation and validation of a fully instrumented Hüttlin HKC 05-TJ laboratory-scale fluidized bed granulator
Drug Dev. Ind. Pharm., 26, (6), 621-634, (2000)

H. C. J. Orth, P. C. Schmidt,
Stability and Stabilization of Hyperforin
Pharm. Ind., 62, 60-62 (2000)

O. Planinšek, R. Pišek, A. Kristl, P. C. Schmidt, S. Srčič
Increased aqueous solubility of N-(7-oxododecanoyl)-L-alanyl-D-isoglutamine by coprecipitating with various pharmaceutical carriers
Acta Pharm., 49, 89-98 (1999)

K. G. Wagner, M. Krumme, T. E. Beckert, P. C. Schmidt
Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press
Eur. J. Pharm. Biopharm., 50, 285-291 (2000)

S. Schmid, C. C. Müller-Goymann, P. C. Schmidt
Interactions during aqueous film coating of ibuprofen with Aquacoat ECD
Int. J. Pharm., 197, 35-39 (2000)

T. Gebre-Mariam, P. C. Schmidt
Sustained release chloroquine phosphate from hard gelatin capsules filled with thermosoftening polyethylene glycol-cetostearyl alcohol matrices
Ethiop. Pharm. J., 16, 1-11 (1998)

P. C. Schmidt
Kollidon® (Polyvinylpyrrolidone): A review on ist use in granulation
BASF exact, No. 2, July 1999

S. Heinrich, L. Mörl, K. Wöstheinrich, P. C. Schmidt
Non-stationary drying kinetics in a discontinuous pharmaceutical fluidized bed coating process
Drying Technology, 18, 2065-2090 (2000)

H. M. Cabral Marques, P. C. Schmidt
The in vitro deposition of respirable fraction of dry powder inhalations by laser diffractometry and inertial impaction
Pharmazie, 57, 546-551, (2002)

H. Bauer, T. Herkert, M. Bartels, K.-A. Kovar, E. Schwarz, P. C. Schmidt
Investigations on polymorphism of mannitol/sorbitol mixtures after spray-drying using differential scanning calorimetry, X-ray diffraction and Near-Infrared Spectroscopy
Pharm. Ind., 62, 231-235 (2000)

J. Dressler, P. C. Schmidt, M. Bättig, B. Luy, H. Krämer
Reinigungsvalidierung von Tablettenpressen – immer noch ein Problem?
Swiss Pharma, 22, (6), 5-12 (2000)

K. G. Wagner, M. Krumme, P. C. Schmidt
Pellet containing tablets Examination of distribution and deformation behaviour
S. T. P. Pharma, 10, 327-334 (2000)

P. C. Schmidt, H. Römpp
Resistance to crushing of tablets: Do we need a more precise description of the method in the European Pharmacopoeia?
Pharmeuropa, 12, 573-583 (2000)

S. Schmid, M. A. Wahl, P. C. Schmidt
Enteric coating of ibuprofen crystals using modified methacrylate copolymers
Pharm. Ind., 62, 635-641 (2000)

S. Schmid, M. A. Wahl, P. C. Schmidt
Enteric coating of ibuprofen crystals using modified methacrylate copolymers
Drugs made in Germany 44, 12-18 (2000)

K. Wöstheinrich, P. C. Schmidt
Polymorphic changes of thiamine hydrochloride during granulation and tableting
Drug Dev. Ind. Pharm., 27, (6), 481-490, (2001)

H. Bauer, M. Bartels, E. Schwarz, P. C. Schmidt
Particle design by surface modifications: spray drying and co-granulation of mannito/sorbitol-mixtures
S. T. P. Pharma, 11, 203-209 (2001)

B. Schulz, S. Stoeva, W. Voelter, P. C. Schmidt
Proteinanalytische Untersuchungen an Enzymtabletten
Pharmazie, 56, 704-710 (2001)

S. Schmid, P. C. Schmidt
Fast dispersible ibuprofen tablets
Eur. J. Pharm. Sciences, 15, 295-305 (2002)

P. C. Schmidt
Arzneiformendesign für den Urogenitaltrakt
Pharm. Ztg., 146, 2092-2096 (2001)

J. A. Dressler, K. G. Wagner, M. A. Wahl, P. C. Schmidt
Comparison of incremental and inductive displacement transducers on an eccentric tablet press
Pharm. Ind., 63, (8) 886-893 (2001)

J. A. Dressler, K. G. Wagner, M. A. Wahl, P. C. Schmidt
Comparison of incremental and inductive displacement transducers on an eccentric tablet press
Drugs made in Germany, 44, (3) 70-77 (2001)

C. S. Kaiser, H. Römpp, P. C. Schmidt
Pharmaceutical applications of supercritical carbon
Pharmazie, 56, (12) 907-926, (2001)

S. v. Eggelkraut-Gottanka, S. Abu Abed, W. Müller, P. C. Schmidt
Quantitative analysis of active components and by-products of eight dry extracts form Hypericum perforatum L. (St. John's Wort)
Phytochemical analysis, 13, 170-176 (2002)

S. v. Eggelkraut-Gottanka, S. Abu Abed, W. Müller, P. C. Schmidt
Roller compaction and tabletting of St. John's wort plant dry extract using a gap width and force controlled roller compactor. 1. Granulation and tabletting of eight different extract batches
Pharm Dev. Technol., 7, 433-445, (2002)

S. v. Eggelkraut-Gottanka, S. Abu Abed, W. Müller, P. C. Schmidt
Roller compaction and tabletting of St. John's wort plant dry extract using a gap width and force controlled roller compactor. 2. Study of roller compaction variables on granule and tablet properties by a $3^3$ factorial design
Pharm Dev. Technol., 7, 447-455, (2002)

K. J. Waleczek, B. Hempel, P. C. Schmidt
Preparation and stability of a camomile ointment containing a supercritical carbon dioxide chamomile extract/ß-cyclodextrin inclusion complex

S. T. P. Pharma Sciences, 12 (5), 329-333 (2002)

K. J. Waleczek, H. M. Cabral Marques, B. Hempel, P. C. Schmidt
Phase solubility studies of pure (-)-α-bisabolol and camomile essential oil with ß-cyclodextrin
Eur. J. Pharm. Biopharm., in press

A. Endale,P. C. Schmidt, T. Gebre-Mariam
Quantitative determination of saponins in the extracts of the seeds of glinus lotoides using calorimetric and UV-spectrophotometric methods
Ethiop. Pharm. J., 18, 1-14 (2000)

M. Schiller, H. von der Heydt, F. März, P. C. Schmidt
Quantification of sugars and organic acids in hygroscopic pharmaceutical herbal dry extracts by several chromatographic methods
J. Chromatography A, 18, 1-14 (2002)

M. Schiller, P. C. Schmidt,
Arzneistoffe zum Aufkleben
Pharm. Ztg., 147, 2348-2352 (2002)

M. Schiller, H. von der Heydt, F. März, P. C. Schmidt
Enhanced processing properties and stability of film coated tablets prepared from roller-compacted and ion-exchanged *Escholtzia californica* Cham. Dry extracts
S. T. P. Pharma, in press

I. Rager, G. Roos, P. C. Schmidt, K.-A. Kovar
Rapid quantification of constituents in St. John's wort extracts by NIR spectroscopy
J. Pharm. Biomedical Analysis, 28, 439-446 (2002)